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Promoted Preparation of Aminophosphonate and Functionalized Coumarins Derivatives as Key Constituent of Many Pharmaceutical Compounds

Helia Mohammadi, Bita Mohtat*, Mehran Kordtabar

Department of Chemistry, Karaj Branch, Islamic Azad University, Karaj, Iran

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Abstract

The reaction between trialkyl phosphites with dialkyl actylenedicarboxylates in the presence of 2-hydroxyquinoline (2-quinolinol) leads to β-aminophsphonates derivatives which they have many applications in medicinal chemistry. When the reaction was performed by triphenylphosphite, a new pyrano quinoline compounds were obtained in fairly good yields. These compounds also provide biologically interesting. All products were established by IR, NMR (^{1}H, ^{13}C and ^{31}P), mass spectroscopy and elemental analysis.

***Keywords*:** β-aminophsphonates,Coumarins, Trialkyl (aryl) phosphate, 2-quinolinol,Dialkyl actylenedicarboxylates.

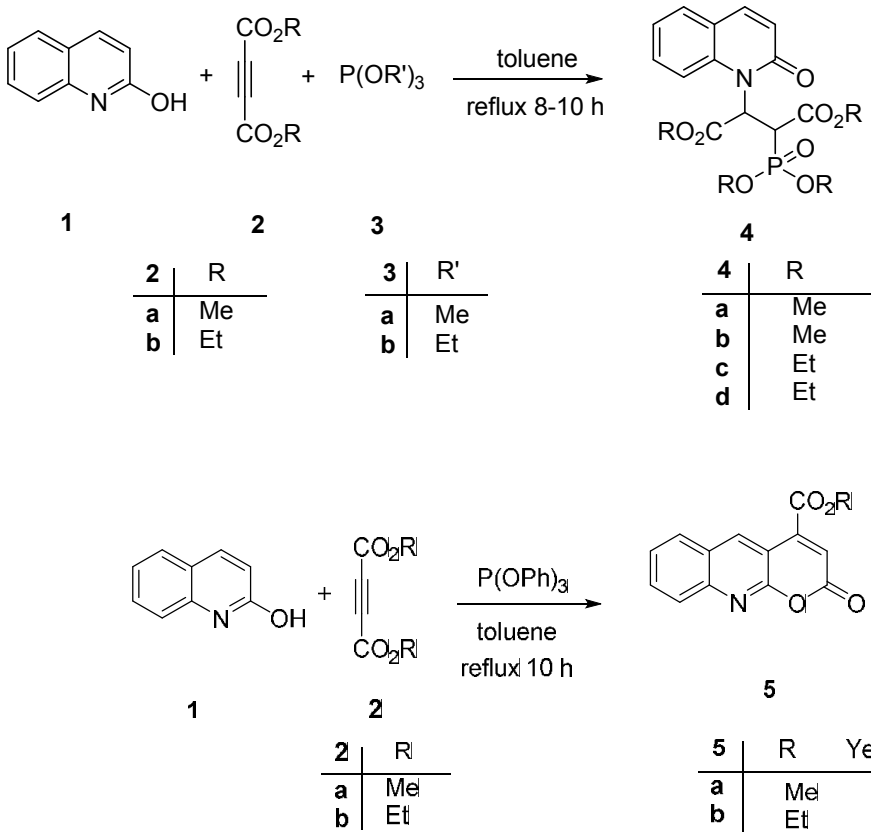
* ***Corresponding author:*** *Bita Mohtat, Department of Chemistry, Karaj Branch, Islamic Azad University, Karaj, Iran. E-mail:b_mohtat@yahoo.com.*

Introduction

Amino phosphonates are very important compounds in biological processes, because they have structural analogues of the corresponding acids and transition state mimics in hydrolysis of peptides [1-4]. In addition, they have achieved significant role since wide applications not only in agriculture but also in biological and medicinal chemistry, as enzyme inhibitors, HIV protease, antibiotics, herbicides, fungicides, and insecticides. Besides, their important uses for antibody generation are well documented [5-11]. The preparation of phosphonate ester compounds involving two chiral centers via a one-pot reaction methodology is well established [12-16]. The P=O group has often been incorporated into the compounds to enhance their thermal oxidative stability and ignition resistance [17].

On the other hand, coumarins are a class of lactones, which are indispensable heterocyclic units to both the chemists and the biochemists [18]. Several coumarin derivatives have been reported for their significant anti-inflammatory activities and their ability to inhibit these enzymes in inhibiting inflammation [19-21]. Interest in coumarins as antibiotics is due to the recent observations that these are potent inhibitors of bacterial DNA gyrase, which is involved in cell growth [22-26].

In addition, multicomponent reactions have received considerable attention because of their wide range of applications inorganic and medicinal chemistry for the creation of structural diversity and combinatorial libraries [27]. In recent years, the use of multicomponent reactions has emerged as a powerful and efficient tool for the synthesis of structurally diverse molecules. There are many studies on the multicomponent reaction between trivalent phosphorus nucleophiles and, α,β-unsaturated carbonyl compounds in the presence of C–H, O-H or N–H acids to produce phosphonate ester or functionalized coumarins [28-31]. Here we report the preparation of these two types of compounds via three component reactions between 2-hydroxy quinoline (2-quinolinol) dialkyl acetylene dicarboxylate in the presence of trialkyl (aryl) phosphite (scheme 1).



Scheme 1. Atypical procedure for the synthesis of **4** and **5.**

Experimental

General

Dialkyl acetylenedicarboxylate, trialkyl phosphite and 2-quinolinol were purchased from Merck (Germany) and Fluka (Switzerland) and were used as received. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-460 spectrometer using KBr disc. Elemental analyses for C, H, and N were performed usinga Heraeus CHN–O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured ($CDCl_3$ solution and using TMS (tetramethylsilane) as an internal standard) with a Bruker DRX-300 AVANCE spectrometer at 300, 75.5 and 121.5 MHz, respectively.

*Procedure for preparation of compounds **4a-d**and **5a-b***

To a magnetically stirred solution of trialkyl(aryl) phosphite (2 mmol) and 2-hydroxyquinoline (2 mmol) in toluene (15 ml) was added dropwise a mixture of dialkyl acetylenedicarboxylate (2 mmol) in toluene (3 ml) at room temperature over 2 min. The reaction mixture was then refluxed and stirred for 8-10 h. Upon completion of reaction by thin layer chromatography(TLC)using n-hexane-

ethyl acetate (3:1) mixture, the solvent was removed under reduced pressure and the residue was purified by thin layer chromatography on precoated silica gel 20×20 glass plates (60 F254, 0.25 mm thickness, Merck) visualized under Ultraviolet (UV) lamp.

Dimethyl 2-(dimethoxyphosphoryl)-3-(2-oxoquinolin-1(2H)-yl)succinate **(4a)**

White powder, yield: 0.70 g (88%), m.p. 140-142 ℃. IR (KBr, cm^{-1}): 1258(P=O), 1595 (C=N), 1661 (C=O amide), 1746(C=O ester). ^{1}HNMR (300MHz, $CDCl_3$):δ3.40 (6H, d, $^3J_{HP}$ = 11.1 Hz, $2OCH_3$), 3.66 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.71 (1H, dd, $^3J_{HH}$ = 10.3 Hz, $^2J_{HP}$ = 20.9 Hz, CHC*H*P=O), 5.93 (1H, dd, $^3J_{HH}$ = 10.3 Hz, $^3J_{HP}$=3.6 Hz, C*H*CHP=O), 6.64 (1H, d, $^3J_{HH}$ = 9.5 Hz, CH), 7.25 (1H, t, $^3J_{HH}$ = 7.8 Hz, CH), 7.69-7.58 (2H, m, 2CH), 7.74 (1H, d, $^3J_{HH}$ = 9.5 Hz, CH) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ42.8 (d, $^1J_{CP}$ = 127.6 Hz, CHP), 53.1 (d, $^2J_{CP}$ = 14.5 Hz, $2OCH_3$), 53.2 (OCH_3), 55.1 (OCH_3), 120.1 (CH), 121.1 (CH), 122.6 (CH), 129.2 (CH), 130.5 (C), 139.5 (CH), 140.8 (CN), 163.0 (C=O $_{amid}$), 168.5 (d, $^3J_{CP}$ = 6.9 Hz, C=O $_{ester}$), 169.0 (d, $^2J_{CP}$ = 17.6 Hz, C=O $_{ester}$) ppm.^{15}P NMR (102.5 MHz, $CDCl_3$): δ 21.55 ppm. MS (EI) *m*/*z*: 397 (M^+, 68), 333 (65), 306 (68), 289 (100), 256 (87), 170 (54), 145 (72), 128 (63), 109 (45). Anal. Cal. For $C_{17}H_{20}NO_8P$: C, 51.39; H, 5.07; N, 3.53%. Found: C, 51.59; H, 5.02; N, 3.54%.

Dimethyl 2-(diethoxyphosphoryl)-3-(2-oxoquinolin-1(2H)-yl)succinate **(4b)**

White powder, yield: 0.68 g (81%), m.p. 137-139℃. IR (KBr, cm^{-1}): 1258(P=O), 1595 (C=N), 1661 (C=O amide), 1746(C=O ester). ^{1}HNMR (300MHz, $CDCl_3$):δ1.00 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 1.09 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.65 (3H, s, OCH_3), 3.73-3.86 (4H, m, $2OCH_2$), 3.88 (3H, s, OCH_3), 4.69 (1H, dd, $^3J_{HH}$ = 10.4 Hz, $^2J_{HP}$ = 20.7 Hz, CHC*H*P=O), 5.93 (1H, dd, $^3J_{HH}$ = 10.4 Hz, $^3J_{HP}$ = 3.0 Hz, C*H*CHP=O), 6.62 (1H, d, $^3J_{HH}$ = 9.5 Hz, CH), 7.25 (1H, t, $^3J_{HH}$ = 7.65 Hz, CH), 7.56-7.62 (2H, m, 2CH), 7.75 (1H, d, $^3J_{HH}$ = 7.4 Hz, CH), 7.73 (1H, d, $^3J_{HH}$ = 9.3 Hz, CH) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ15.9 (d, $^3J_{CP}$ = 5.5 Hz, CH_3), 16.0 (d, $^3J_{CP}$ = 5.6 Hz, CH_3), 43.8 (d, $^1J_{CP}$ = 130.1 Hz, CHP), 53.0 (OCH_3), 53.1 (OCH_3), 55.2 (d, $^3J_{CP}$ = 4.8 Hz, CH), 62.8 (d, $^2J_{CP}$ = 7.1 Hz, OCH_2), 62.9 (d, $^2J_{CP}$ = 6.4 Hz, OCH_2), 115.0 (CH), 121.1 (CH), 122.2 (CH), 122.5 (CH), 129.1 (CH), 130.4 (C), 139.7 (CH), 140.6 (CN), 163.0 (C=O $_{amide}$), 168.7 (d, $^3J_{CP}$ = 7.0 Hz, C=O $_{ester}$), 169.1 (d, $^2J_{CP}$ = 17.7 Hz, C=O $_{ester}$) ppm.^{15}P NMR (102.5 MHz, $CDCl_3$):δ 18.07 ppm. MS (EI) *m*/*z*: 425 (M^+, 87), 336 (53), 289 (100), 256 (79), 170 (24), 221 (34), 152 (63), 145 (61), 137 (33).Anal. Cal. For $C_{19}H_{24}NO_8P$: C, 53.65; H, 5.69; N, 3.29%. Found: C, 53.49; H, 5.71; N, 3.27%.

Diethyl 2-(dimethoxyphosphoryl)-3-(2-oxoquinolin-1(2H)-yl)succinate **(4c)**

White powder, yield: 0.64 g (76%), m.p. 151-153 ℃. IR (KBr, cm^{-1}): 1262(P=O), 1596 (C=N), 1659 (C=O amide), 1734(C=O ester), 1755 (C=O ester). ^{1}HNMR (300MHz, $CDCl_3$):δ1.17 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 1.40 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.39 (3H, d, $^2J_{HP}$ = 9.5 Hz, OCH_3), 3.43 (3H, d, $^2J_{HP}$ = 9.5 Hz, OCH_3), 4.10-4.40 (4H, m, $2OCH_2$), 4.74 (1H, dd, $^3J_{HH}$ = 10.4 Hz, $^2J_{HP}$ = 21.0 Hz, CHC*H*P=O), 5.93 (1H, dd, $^3J_{HH}$ = 10.3 Hz, $^3J_{HP}$=3.6 Hz, C*H*CHP=O), 6.66 (1H, d, $^3J_{HH}$ = 9.4 Hz, CH), 7.58-7.69 (3H, m, 3CH), 7.74 (1H, d, $^3J_{HH}$ = 9.5 Hz, CH) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ14.1 (CH_3), 14.4 (CH_3), 43.5 (d, $^1J_{CP}$ = 128.4 Hz, CHP), 50.5 (d, $^3J_{CP}$ = 4.2 Hz, CH), 53.4 (d, $^2J_{CP}$ = 14.5 Hz, $2OCH_3$), 61.3 (OCH_2), 62.7 (OCH_2), 118.9 (CH), 120.4 (CH), 121.8 (CH), 124.2 (CH), 128.1 (C), 134.9 (CH), 140.1 (CN), 162.2 (C=O $_{amid}$), 169.2 (d, $^3J_{CP}$ = 6.6 Hz, C=O $_{ester}$), 170.6 (d, $^2J_{CP}$ = 17.2 Hz, C=O $_{ester}$) ppm.^{15}P NMR (102.5 MHz, $CDCl_3$):δ 20.51 ppm.MS (EI) *m*/*z*: 425 (M^+, 87), 363 (45), 317 (100), 282 (71), 170 (37), 145 (61), 109 (42).

Diethyl 2-(diethoxyphosphoryl)-3-(2-oxoquinolin-1(2H)-yl) succinate **(4d)**

White powder, yield: 0.59 g (65%), m.p. 158-160 ℃. IR (KBr, cm^{-1}): 1258(P=O), 1595 (C=N), 1661 (C=O amide), 1746(C=O ester), 1759 (C=O ester). ^{1}HNMR (300MHz, $CDCl_3$):δ1.03 (3H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.07 (3H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.14 (3H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.38 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 4.11-4.25 (6H, m, $2OCH_2$), 4.32-4.35 (2H, m, OCH_2), 4.67 (1H, dd, $^3J_{HH}$ = 10.4 Hz, $^2J_{HP}$ = 20.7 Hz, CHC*H*P=O), 5.97 (1H, dd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HP}$=3.8 Hz, C*H*CHP=O CH), 6.65 (1H, t, $^3J_{HH}$ = 9.5 Hz, CH), 7.56-7.60 (3H, m, 3CH), 7.71-7.75 (2H, m, 2CH) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ13.8 (CH_3), 14.7 (CH_3), 15.6 (d, $^3J_{CP}$ = 5.7 Hz, CH_3), 16.1 (d, $^3J_{CP}$ = 5.7 Hz, CH_3), 44.1 (d, $^1J_{CP}$ = 127.1 Hz, CHP), 50.7 (d, $^3J_{CP}$ = 4.8 Hz, CH), 61.6 (OCH_2), 63.0 (OCH_2), 119.4 (CH), 120.9 (CH), 121.2 (CH), 124.5 (CH), 128.8(C), 135.3 (CH), 140.7 (CN), 162.5 (C=O $_{amid}$), 169.8 (d, $^3J_{CP}$ = 6.7 Hz, C=O $_{ester}$), 170.0 (d, $^2J_{CP}$ = 17.0 Hz, C=O $_{ester}$) ppm.^{15}P NMR (102.5 MHz, $CDCl_3$):δ 21.75 ppm.MS (EI) *m*/*z*: 453 (M^+, 54), 363 (32), 336 (69), 317 (100), 310 (61), 180 (70), 170 (58), 145 (61), 137 (48). Anal. Cal. For $C_{21}H_{28}NO_8P$: C, 55.63; H, 6.22; N, 3.09%. Found: C, 55.74; H, 6.25; N, 3.08%.

Methyl 2-oxo-2H-pyrano[2,3-b]quinoline-4-carboxylate **(5a)**

Yellow powder, yield m.p. 118-120 ℃. IR (KBr, cm^{-1}): 1591 (C=N), 1721(C=O lactone), 1743 (C=O ester). ^{1}HNMR (300MHz, $CDCl_3$):δ3.85 (3H, s, OCH_3), 7.05 (1H, s, CH), 7.15 (2H, m, 2CH), 7.27 (1H, t, $^3J_{HH}$ = 7.4 Hz, CH), 7.41 (2H, m, 2CH).^{13}C NMR (75 MHz, $CDCl_3$): δ52.4 (OCH_3), 121.4 (C), 123.2 (CH), 123.7 (C), 124.8 (CH), 126.5 (CH), 129.6 (CH), 134.1 (CH), 134.80 (CH), 145.8 (C), 150.3 (C=N), 163.3 (C=O), 165.2 (C=O), 174.4 (O-C=N).MS (EI) *m*/*z*: 255

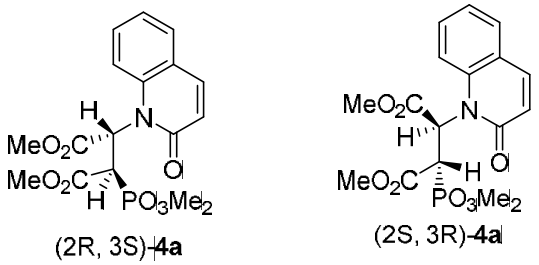
(M^+,27), 196 (100), 128 (75), 59 (67).Anal. Cal. For $C_{14}H_9NO_4$: C, 65.88; H, 3.55; N, 5.49%. Found: C, 66.07; H, 3.56; N, 5.47%.

Ethyl 2-oxo-2H-pyrano[2,3-b]quinoline-4-carboxylate **(5b)**

Yellow powder, m.p. 125-127 ℃. IR (KBr, cm^{-1}): 1593 (C=N), 1726(C=O lactone), 1748 (C=O ester). ^{1}HNMR (300MHz, $CDCl_3$):δ1.35 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 4.31 (2H, t, $^3J_{HH}$ = 7.1 Hz, OCH_2), 7.04 (1H, s, CH), 7.10 (1H, t, $^3J_{HH}$ = 8.7 Hz, CH), 7.16-7.23 (2H, m, 2CH), 7.31-7.49 (2H, m, 2CH).^{13}C NMR (75 MHz, $CDCl_3$): δ14.2 (CH_3), 61.7 (OCH_2), 122.0 (C), 123.4 (CH), 123.8 (C), 124.7 (CH), 126.8 (CH), 128.0 (CH), 130.2 (CH), 135.9 (CH), 145.5 (C), 150.9 (C=N), 160.8 (C=O), 1.268.2 (C=O), 174. 6 (O-C=N). MS (EI) *m/z*: 269 (M^+,18), 196 (100), 142 (63), 73 (47).Anal. Cal. For $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20%. Found: C, 66.71; H, 4.13; N, 5.22%.

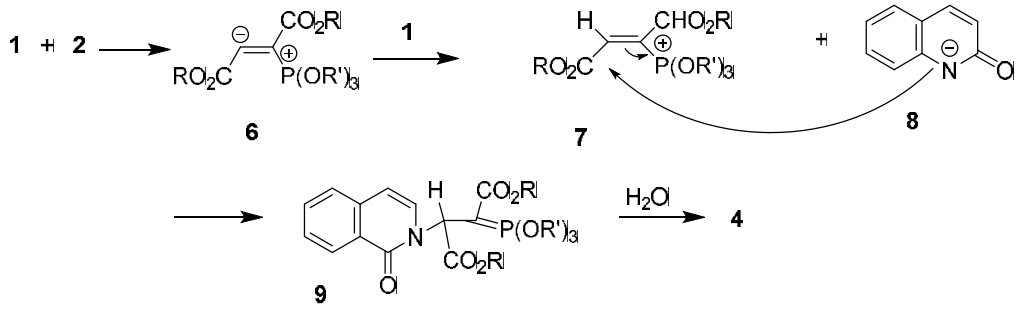
Results and discussions

The reaction were carried out and completed within 8-12h. Products **4a-d** and **5a-b** were all new and deduced on the basis of their ^{1}H,^{13}C, ^{31}PNMR and IR spectra among with mass spectroscopic data and elemental analyses. The mass spectrum of **4a** showed the molecular ion peak at m/z= 397. The IR spectrum of **4a** showed absorption bands at 1661 and 1746 cm^{-1}due the carbonyl groups. The P=O group appears at 1258 cm^{-1}.The^{1}HNMR spectrum of **4a** exhibited methoxy groups of phosphonate (δ: 340 ppm with $^3J_{HP}$ = 11.1 Hz) as doublets. The two singlets peak for methoxy protons of esters are shown at 3.66 and 3.89 ppm. Two doublet of doublet signals at 4.71 and 5.93 ppm are belong to CHCHP=O moiety. The aromatic protons resonated between 6.64 and 5.93 ppm. Singlets and doublets peaks (split with phosphorus), in ^{13}C NMR spectrum are in agreement with the proposed structure. The vicinal proton-proton coupling constant can help to determine the proton position. The comparison of $^3J_{CP}$ for carbonyl group indicates the geometry of the products. Observation of $^3J_{HH}$ = 10.3 in **4a** indicates an anti-arrangement for the vicinal protons. Since compound **4a** possesses two stereogenic centers, two diastereomers with anti HCCH arrangement are possible (Scheme 2). The observation of $^3J_{CP}$= 17.6 Hz for the carbonyl carbon atom of CO_2Me group is in agreement with the (2S,3R) or (2R,3S) diastereomer.



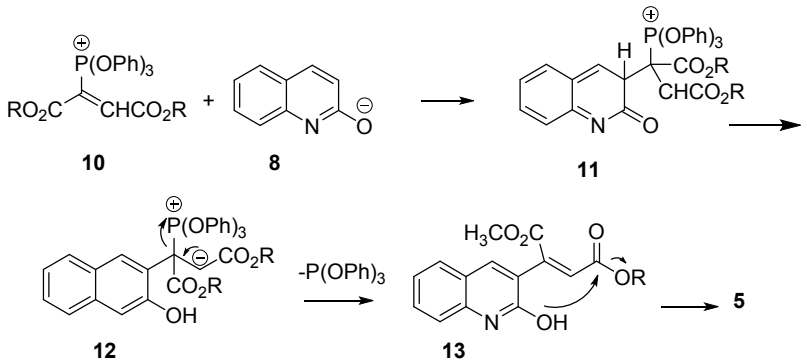
Scheme 2. Two enantiomers of phosphonate **4a.**

A possible mechanism is proposed in scheme 3. At first l:l addition was occurred between trialkylphosphite and dialkylactylenedicarbonylate to produces **6** and then protonated by 2-hydronyquinoline. The vinyl phosphophosphonium **7** is attacked by conjugate addition of anion **8** which leads to phosphite ylide **9** which is hydrolyzed to give **4**.



Scheme 3. A plausible mechanism for formation of **4.**

Mechanistically the reaction involved the formation of zwitterion intermediate between $(PhO)_3P$ and **2** subsequent protonation by **3** which followed by anelectrophilic attack of vinylphenoxyphosphonium cation **10** on the romantic rain at the 3-position relative to the strong activation group **11**. This intermediate undergoes [1-3]-H shift to furnish **12** which converted to **13** by the loss of $(PhO)_3P$. The product **5** is presumably produced by intramolecular lactonization of the unsaturated diester (Scheme 4).



Scheme 4. A plausible mechanism for formation of **5**

Conclusion

In conclusion, we have described a one pot three component synthesis of functionalized amino phosphonates and as coumarins. The present procedure has the advantage that the reaction is performed under catalysis-free condition, high yields, an elegant technique for C-P bond formation and starting materials can be used without any activation or modification. The antifungal activity of **4a-d** and antibacterial effect of **5a-b** is under evaluation.

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